Remarks

A. Amendments to the Specification

The specification was amended at three sections:

- the paragraph beginning at line 3, page 28;
- the paragraph beginning at line 17, page 28; and
- the paragraph beginning at line 20, page 28.

The amendments to each of the above-cited paragraphs correct typographical errors present in the chemical structures depicted in the schemes. No new matter has been introduced by any of these amendments.

B. Amendments to the Claims

Claims 6, 7, 20 to 22 and 31 to 42 have been amended. The amendments to claims 6 and 7 were made to better describe the claimed invention. The amendments to claims 20 to 22 correct a typographical error. The amendments to claims 31 to 42 limit the claims to disease states mediated by tyrosine kinase. No new matter has been introduced by any of the claim amendments. Applicants reserve the right to pursue the subject matter excluded by the amendments to claims 31 to 42 in a continuation application.

1. Rejection under 35 U.S.C. § 112, second paragraph

Claims 6-16 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts the following:

(1) the recitation of "one of" in claims 6 and 7 is vague and unclear as to what choice is to be made;

(2) the recitation of "and pharmaceutically acceptable salts thereof" in claims 6-10 makes it unclear whether these claims are compound claims or composition claims with this limitation; and the Markush recitation should be in the alternate form and in singular; and

(3) the recitation of "a 1,3,5-triazine" in claims 11-16 makes it unclear as to what triazine is being used as a starting material for the displacement reaction embraced by these claims. According to the Examiner, it is not clear what group is to be displaced.

Regarding rejection (1), Applicants have amended claims 6 and 7 to the following format: "A compound of Formula __ according to claim __ selected from...."

Regarding rejection (2), Applicants have amended claims 6 and 7 to recite "or a pharmaceutically acceptable salt thereof." Applicants note that contrary to the Examiner's assertion, claims 8-10 do not recite the phrase "and pharmaceutically acceptable salts thereof." Therefore, these claims have not been amended.

Regarding rejection (3), Applicants respectfully disagree with the Examiner that the recitation of a 1,3,5-triazine renders these claims indefinite. Claims 11-16 are directed toward methods of preparing compounds of known structures (*i.e.*, Formulae I-IV). For example, it is clear that in Formula I, the triazine ring contains 3 substituents: a "R" group, a "A_1R_1N" group and a "$(A_2R_3)R_2N$" group at the 2-, 4-, and 6- positions of the ring. A reading of claim 11, for example, which is directed to the preparation of a compound of Formula I or Formula III indicates that R is OH and that 3 substituents are added to the triazine ring: a -OH group and two amino groups at the 2-, 4-, and 6- positions of the ring, where each of the amino groups is a primary or secondary alkyl or aromatic amine. Because the structure of the final product is known, the recited steps for preparing that structure would be clearly understood by a person of ordinary skill in the art.

At least in light of these amendments and arguments, Applicants respectfully request that the rejections of the identified claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

2. Rejection under 35 U.S.C. § 112, first paragraph

A. hydrates and solvates

Claims 1-44 are rejected because the Examiner asserts that Applicants' specification, while being enabling for making pharmaceutically acceptable salts, does not reasonably provide enablement for making hydrates or solvates. In evaluating the enablement issue for hydrates and

solvates, the Examiner conducts a brief analysis of the factors cited in *In re Wands*, 8 USPQ2d 1400.

Applicants respectfully disagree with the Examiner's rejection of claims 1-44 as not being enabled for hydrates and solvates of the compounds of Formulae I through IV. The Examiner cites West (Solid State Chemistry) as teaching that a solvate (which the Examiner equates with a hydrate) is an "interstitial solid solution" and that it is not usually possible to predict whether solid solutions will form. The sections of West that the Examiner refers to for support are limited to inorganic structures. An exemplary solid solution is listed as the combination of Al_2O_3 and Cr_2O_3 at high temperatures. Properties such as ferromagnetism and conductivity, which are described as being modified upon the formation of solid solutions, are generally associated with inorganic compounds. In fact, there is no indication that the information disclosed on page 358 and 365 of West have any relevance to strictly organic systems.

Further, the Examiner cites Vippagunta in an Advanced Drug Delivery Reviews article as teaching that the formation of hydrates is unpredictable. Applicants point out to the Examiner that in section 3.1 of Vippagunta at page 15, it is stated that "it has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates." With fully 33% of pharmaceutical compounds having the ability to form crystalline hydrates, Applicants assert that it would certainly be proper to include hydrates as within the scope of protection of the compound claims. Moreover, the 33% estimation for crystalline hydrates does not include non-crystalline hydrates. Accordingly, the percentage of pharmaceutical compounds capable of forming any hydrate, would likely be signficantly higher than 33%. Because Applicants don't limit the claimed hydrates to a crystalline form, the rationale for including hydrates in the claims is therefore even stronger. In addition, Vippagunta states on page 20 that various processes, such as freeze-drying, are known and used in the prior art for obtaining hydrates.

For at least the reasons discussed above, Applicants respectfully request that this rejection of the identified claims be withdrawn.

B. disease states

Claims 17-42 are rejected because the Examiner asserts that Applicants' specification, while being enabling for treating breast cancer, does not reasonably provide enablement for inhibition of any or all tyrosine kinases, any or all cancers, any or all vascular diseases, or any or all ocular diseases. As before, the Examiner conducts a brief analysis of the *In re Wands* factors in assessing enablement.

Applicants respectfully disagree with the Examiner's rejection of the claims 17-42 as not being enabled for disease states other than breast cancer for at least the following reasons:

Claims 20, 21 and 22 are directed to a method of inhibiting protein kinase activity *in vitro*. The pharmacological examples on pages 41-44 of the specification demonstrate that a representative number of compounds of the invention show activity in the KDR Enzymatic Assay as well as in the KDR Cell-Based Assay. Given that these assays are carried out under *in vitro* conditions, it would seem clear that these claims are fully enabled by the specification.

Claims 23, 24 and 25 are directed to a method of inhibiting protein kinase activity in cells. The pharmacological example on page 42 shows that a representative number of compounds of the invention show activity in the KDR Cell-based Assay. Accordingly, it would seem clear that these claims are also enabled by the specification.

Claims 17, 18 and 19 are directed to a method of inhibiting protein activity comprising contacting the kinase with an effective inhibitory amount of the compounds of the invention. It would seem clear that *in vitro* assay data obtained on both an enzymatic level and a cellular level for a representative number of active compounds, would be sufficient to provide enablement for these claims.

Claims 26, 27 and 28 are directed to a method of inhibiting tyrosine kinase activity in a mammal. Applicants point the Examiner to page 42 of the specification where it states that the cells tested in the KDR Cell-Based Assay were human cells (*i.e.*, human umbilical vein endothelial cells (HUVEC)). Thus, the cells in which the compounds of the invention show activity are mammalian cells. In view of the fact that these compounds are acting upon cells which are present in a mammalian body, Applicants assert that a person of ordinary skill in the

art would find that Applicants' specification does enable "a method for inhibiting protein kinase activity in a mammal."

Claims 29 and 30 are limited to particular types of tyrosine kinases: VEGFR-2 (which is KDR), c-fms, c-met or tie-2. Because Applicants are of the opinion that claim 17 (from which claim 29 depends) and claim 26 (from which claim 30 depends) are enabled, Applicants assert that claims 29 and 30 are also enabled.

Applicants do not agree with the Examiner regarding the alleged lack of enablement of claims 31 to 42. However, in order to expedite prosecution of the subject application, these claims have been amended to indicate that the particular recited disease state(s) to be treated are disease state(s) that are mediated by tyrosine kinase.

For at least the reasons discussed above, Applicants respectfully request that this rejection of the identified claims be withdrawn.

3. Conclusion

Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's rejections. Accordingly, all claims are believed to be in proper form in all respects and a favorable action on the merits is respectfully requested. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is invited to contact Applicants' undersigned representative to expedite prosecution.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,

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